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<http://dx.doi.org/10.1289/EHP151>

Received: 14 December 2015

Revised: 13 February 2016

Accepted: 6 May 2016

Published: 10 June 2016

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# **Male Breast Cancer Incidence and Mortality Risk in the Japanese Atomic Bomb Survivors – Differences in Excess Relative and Absolute Risk from Female Breast Cancer**

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**Running title:** Male breast cancer incidence and mortality in LSS

**Acknowledgments:** The authors are grateful for the detailed and helpful comments of Professor John Cherrie, Professor Keith Palmer, Dr Dale Preston, and the three referees. This report makes use of data obtained from the Radiation Effects Research Foundation (RERF) in Hiroshima and Nagasaki, Japan. RERF is a private, non-profit foundation funded by the Japanese Ministry of Health, Labour and Welfare (MHLW) and the U.S. Department of Energy (DOE), the latter in part through DOE Award HS-DE0000031 to the National Academy of Sciences. The data include information obtained from the Hiroshima City, Hiroshima Prefecture, Nagasaki City, and Nagasaki Prefecture Tumor Registries and the Hiroshima and Nagasaki Tissue Registries. The conclusions in this report are those of the authors and do not necessarily reflect the scientific

judgment of RERF or its funding agencies. This work was supported by the Intramural Research Program of the National Institutes of Health, the National Cancer Institute, Division of Cancer Epidemiology and Genetics.

**Competing financial interests:** Professor McElvenny is a Director at Statistics and Health Limited, a consultancy service to industry and to the legal profession. Professor McElvenny is also listed as a potential expert witness and consultant at the Institute of Occupational Medicine, where he works. As such, Professor McElvenny occasionally does medico-legal work, but has never done any in relation to ionizing radiation exposure and any health outcome. Although there is a potential competing financial interest for Professor McElvenny in relation to the present analysis, in practice there is none.

## Abstract

**Background:** There are well-known associations of ionizing radiation with female breast cancer, and emerging evidence also for male breast cancer. In the UK, female breast cancer following occupational radiation exposure is among that set of cancers eligible for state compensation and consideration is currently being given to an extension to include male breast cancer.

**Objectives:** To compare radiation-associated excess relative and absolute risks of male and female breast cancers.

**Methods:** Breast cancer incidence and mortality data in the Japanese atomic-bomb survivors were analyzed using relative and absolute risk models via Poisson regression.

**Results:** We observed significant ( $p \leq 0.01$ ) dose-related excess risk for male breast cancer incidence and mortality. For incidence and mortality data there are approximate 15-fold and 5-fold elevations, respectively, of relative risk for male compared with female breast cancer incidence, the former borderline significant ( $p = 0.050$ ). In contrast, for incidence and mortality data there are approximate 20-fold and 10-fold elevations, respectively, of female absolute risk compared with male, both statistically significant ( $p < 0.001$ ). There are no indications of differences between the sexes in age/time-since-exposure/age-at-exposure modifications to the relative or absolute excess risk. The probability of causation of male breast cancer following radiation exposure exceeds by at least 5-fold that of many other malignancies.

**Conclusions:** There is evidence of much higher radiation-associated relative risk for male than for female breast cancer, although absolute excess risks for males are much less than for females. However, the small number of male cases and deaths suggests a degree of caution in interpretation of this finding.

## Introduction

Female breast cancer is the most commonly occurring cancer among women in developed and developing regions of the world (World Health Organization (WHO) 2015). Male breast cancer is much rarer - the number of incident cases of male breast cancer is typically about 0.5% - 1% of the number of female breast cancers in many developed western populations (Landis et al. 1999; Office for National Statistics 2012). There is a similar ratio of male breast cancer deaths to female breast cancer deaths (Office for National Statistics (ONS) 2004). Male and female breast cancer share some etiological features, although not all (Weiss et al. 2005).

Female breast cancer has been associated with exposure to moderate and high doses (>100 mGy) of ionizing radiation in the Japanese atomic bomb survivors Life Span Study (LSS) cohort and in women who received radiotherapy (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2008). A pooled analysis of eight cohorts suggested that excess relative risks of female breast cancer are (dependent on cohort) modified by age at exposure or attained age (Preston et al. 2002). There is emerging evidence to suggest that male breast cancer may also be radiogenic, in the LSS incidence dataset (Ron et al. 2005) and in a population-based US case-control study (Thomas et al. 1994). However, possibly due to the small number of cases, Ron *et al.* (Ron et al. 2005) did not report analyses of exposure response trend. There has been no similar study of male breast cancer in the latest LSS mortality follow-up (Ozasa et al. 2012).

In the UK, the Industrial Injuries Advisory Council (IIAC) (Industrial Injuries Advisory Council (IIAC) 2015) is currently considering amending the list of cancers arising from occupational exposure to ionizing radiation for which state compensation may be claimed, if exposure is sufficient to double the relative risk of disease. Included within these considerations is whether

or not to recommend male breast cancer should be added to the list which currently includes female breast cancer and this has provided the motivation for this further analysis. Male breast cancer is currently regarded as a disease for which compensation can be paid if the probability of causation is sufficiently high by the US Department of Labor, and the same relative risk model is used for both sexes (United States Department of Labor 2016). However, the US National Cancer Institute RadRAT probability of causation calculation software does not have a model for male breast cancer (Berrington de Gonzalez et al. 2012).

In this paper we analyze male and female breast cancer incidence and mortality in the latest versions of the LSS incidence (Preston et al. 2007) and mortality data (Ozasa et al. 2012). We assess the statistical comparability of measures of generalized excess relative risk and excess absolute risk between males and females, specifically focusing on dose response trends and their modification by attained age, and age at exposure. Such generalized excess relative and absolute risk models have previously been shown to provide a good description of breast cancer risk in the LSS and in other radiation-exposed groups (Little and Boice 1999; Preston et al. 2002). We shall emphasize estimates of excess relative risk because of their ready applicability to estimate probability of causation (Barabanova et al. 1996).

## Methods

### *Study population and data sources*

The LSS breast cancer incidence data used is the publicly available version of the dataset analyzed by Preston *et al.* (Preston et al. 2007). Details of the study population and methods have been published previously (Preston et al. 2007). The analysis of Preston *et al.* assessed cancer incidence over the years 1958-1998 in the two cities, and this should be roughly comparable with follow-up in the earlier publication of Ron *et al.* (Ron et al. 2005); however, total numbers of

cases differ slightly (see Supplemental Material A Table A2 and Table 1 of Ron *et al.* (Ron et al. 2005), which we discuss later). Likewise, the breast cancer mortality dataset is the publicly available version of the dataset analyzed by Ozasa *et al.* (Ozasa et al. 2012). This analysis assessed mortality over the years 1950-2003. Summary numbers of breast cancer cases, deaths and person years by sex are given in Table 1. Unless otherwise stated, analysis is restricted to those resident in either city (Hiroshima, Nagasaki) at the time of the bombings, and with known breast dose.

### Statistical Methods

Poisson regression methods were used to investigate breast cancer risks. A linear relative risk model was fitted in which the expected number of deaths in stratum  $i$  (defined by certain grouped values of city, sex, attained age and age at exposure) and dose group  $d$  with mean breast dose  $D_{id}$  (in Sv), sex  $s$  ( $\in \{m, f\}$ ) and mean attained age  $a_{id}$ , age at exposure  $e_{id}$  and time since exposure  $t_{id}$  (all in years) is given by:

$$PY_{id}\lambda_i \left(1 + \alpha_s D_{id} \exp[\beta_1[a_{id} - 50]/10 + \beta_2[t_{id} - 30]/10 + \beta_3[e_{id} - 20]/10]\right) \quad (1)$$

where  $PY_{id}$  is the number of person years of follow-up.  $\lambda_i$  is the expected cancer rate in stratum  $i$ , and  $\alpha_s$  is the excess relative risk (ERR) / Sv, both estimated from the model fit, along with all other model parameters ( $\beta_1, \beta_2, \beta_3$ ). The values of 50, 30, 20 years subtracted from the attained age, age at exposure, and time since exposure are the approximate mean values of these variables in the two datasets; we do this to stabilize parameter estimates. Similar models of breast cancer risk have been fitted previously to these and other breast cancer datasets (Little and Boice 1999; Preston et al. 2002; United Nations Scientific Committee on the Effects of Atomic Radiation

(UNSCEAR) 2008). A slight generalization of this model was also fitted, allowing for the adjustment parameters  $\beta_1, \beta_2, \beta_3$  to vary by sex  $s \in \{m, f\}$ :

$$PY_{id} \lambda_i \left( 1 + \alpha_s D_{id} \exp[\beta_{1s}[a_{id} - 50]/10 + \beta_{2s}[t_{id} - 30]/10 + \beta_{3s}[e_{id} - 20]/10] \right) \quad (2)$$

The neutron component of breast cancer dose incorporates a weighting factor (relative biological effectiveness) of 10, to account for the known higher effectiveness of this type of radiation compared with that of high energy gamma rays (International Commission on Radiological Protection 2007).

We also evaluated the excess absolute risk (EAR), modeling of which requires that we construct a parametric function of the baseline (zero dose) risks. We shall assume that the expected number of cases or deaths in stratum  $i$  with certain values of explanatory variables  $(Z_{idj})_{j=1}^N$  (e.g., city, sex, age, time since exposure) is given by:

$$PY_{id} \left( f((Z_{idj})_{j=1}^N, (\gamma_j)_{j=1}^N) + \alpha_s D_{id} \exp[\beta_1[a_{id} - 50]/10 + \beta_2[t_{id} - 30]/10 + \beta_3[e_{id} - 20]/10] \right) \quad (3)$$

or analogous to (2):

$$PY_{id} \left( f((Z_{idj})_{j=1}^N, (\gamma_j)_{j=1}^N) + \alpha_s D_{id} \exp[\beta_{1s}[a_{id} - 50]/10 + \beta_{2s}[t_{id} - 30]/10 + \beta_{3s}[e_{id} - 20]/10] \right) \quad (4)$$

Here the baseline cancer rate is given by:

$$f((Z_{idj})_{j=1}^N, (\gamma_j)_{j=1}^N) = \exp \left[ \sum_{j=1}^N \gamma_j Z_{idj} \right] \quad (5)$$

a function of the explanatory variables and some parameters,  $(\gamma_j)_{j=1}^N$ , the latter determined by the model fit; the contrast with the semi-parametric rates,  $\lambda_i$ , in models (1) and (2) should be noted.

In order to adequately fit breast cancer incidence and mortality, taking account of all factors

other than radiation in the two datasets, we considered models for  $f()$  constructed from a candidate set of variables that included city, sex, all terms  $\ln[age / 50]^k$ ,  $\ln[years \text{ since exposure} / 30]^k$ , and  $[age \text{ at exposure} - 20]^k$  with integral  $k$  between 1 and 6, and all second order interactions of these (e.g., terms of the form  $\ln[age / 50]^3 \times \ln[years \text{ since exposure} / 30]^6$ ). In order to avoid over-parameterized models, the Akaike Information Criterion (AIC) (Akaike 1973, 1981) was employed to select the optimal subset of descriptive variables from this set. AIC penalizes against overfitting by adding 2 x [number of fitted parameters] to the model deviance. A mixed forward-backward stepwise algorithm was used to select the set of variables minimizing AIC, using R (R Project version 3.2.2 2015). The indicated optimal models were augmented to make them polynomially complete, so that if the optimal model included a variable  $A^M B^N$  for some indices  $1 \leq M, N \leq 6$ , then all terms  $A^m B^n$  for indices  $0 \leq m \leq M$ ,  $0 \leq n \leq N$  were also included in the model. The final set of variables in the optimal models for breast cancer incidence and mortality are listed in Supplemental Material B Table B1. Models with parametrically modeled baseline rates of the sort given by expression (4) but using a relative risk formulation were also fitted:

$$PY_{id} f((Z_{idj})_{j=1}^N, (\gamma_j)_{j=1}^N) \left( 1 + \alpha_s D_{id} \exp \left[ \beta_{1s} [a_{id} - 50] / 10 + \beta_{2s} [t_{id} - 30] / 10 + \beta_{3s} [e_{id} - 20] / 10 \right] \right) \quad (6)$$

However, these models are in some ways less flexible than the models (1) and (2) with semi-parametrically modeled baseline rates, and in particular cannot be readily fitted to the male breast cancer data by itself, because there are too few cases. Results are generally similar to those using the semi-parametric relative risk models, so we shall not further refer to them.

In models (1)-(4) we are mainly interested in the excess risk coefficients,  $\alpha_s$ , and in the temporally modifying parameters (by attained age, time since exposure, age at exposure),  $\beta_1, \beta_2, \beta_3$ . Notice that  $t_{id} = a_{id} - e_{id}$  so we only fit sub-models of (1)-(4) with at most two of the three parameters  $\beta_1, \beta_2, \beta_3$  (or  $\beta_{1s}, \beta_{2s}, \beta_{3s}$ ) allowed to be non-zero. All model parameters are estimated via Poisson maximum likelihood (McCullagh and Nelder 1989), using Epicure (Preston et al. 1998). All hypothesis tests are based on the likelihood-ratio test, and unless otherwise stated confidence intervals were based on the profile likelihood (McCullagh and Nelder 1989).

If cancer rate following assumed radiation dose  $D$  is given by  $f((Z_j)_{j=1}^N, (\gamma_j)_{j=1}^N) + g(D)h((Z_j)_{j=1}^N, (\gamma_j)_{j=1}^N)$  for some functions  $f()$ ,  $g()$ ,  $h()$ , then the probability of causation (PC) associated with radiation is given by:

$$\frac{g(D)h((Z_j)_{j=1}^N, (\gamma_j)_{j=1}^N)}{f((Z_j)_{j=1}^N, (\gamma_j)_{j=1}^N) + g(D)h((Z_j)_{j=1}^N, (\gamma_j)_{j=1}^N)} \quad (7)$$

Further details on the rationale are given elsewhere (Barabanova et al. 1996). In particular, when the model is of relative risk form as in expression (1), this simplifies to:

$$\frac{\alpha_s D_{id} \exp[\beta_1[a_{id} - 50]/10 + \beta_2[t_{id} - 30]/10 + \beta_3[e_{id} - 20]/10]}{1 + \alpha_s D_{id} \exp[\beta_1[a_{id} - 50]/10 + \beta_2[t_{id} - 30]/10 + \beta_3[e_{id} - 20]/10]} \quad (8)$$

We estimated PC for male breast cancer using the model fitted here, and compared it with PC estimated for various other sites, using relative risk models fitted by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2008) and by the Biological Effects of Ionizing Radiation VII (BEIR VII) committee (Committee to Assess Health

Risks from Exposure to Low Levels of Ionizing Radiation 2006) to current LSS data, in Supplemental Material A Table A1.

We evaluated PC for attained age 65 (which is approximately the median age of occurrence for male breast cancer in the LSS), assuming exposure to 50 mSv at 35 and 55 years of age.

Although 50 mSv is about twice the mean lifetime cumulative dose, 24.9 mSv, in the UK National Registry for Radiation Workers, there are 20,373 workers (11.7% of the cohort) with cumulative doses above this level (Muirhead et al. 2009).

## Results

There are a total of 7 incident cases of male breast cancer, and 6 male breast cancer deaths (Table 1). There are 847 female breast cancer cases, and 324 female breast cancer deaths, which are some 100- to 50-fold greater than the corresponding male figures, respectively. Crude breast cancer incidence rates are about 70-fold higher ( $64.89 / 0.90$ ) in women than men, and breast cancer mortality rates about 34-fold higher ( $16.09 / 0.47$ ) (Table 1). Table 2 demonstrates that most cases and deaths are above the age of 60 years (4/7 cases, 5/6 deaths). Most also occur among the younger age exposure groups, under exposure age 40 years (5/7 cases, 5/6 deaths).

There are highly statistically significant trends with dose for male breast cancer incidence ( $p=0.003$ )(Table 3). The breast cancer incidence excess relative risk for males adjusted for the effect of attained age and age at exposure is  $27.68 \text{ Sv}^{-1}$  (95% CI 1.81, 90.16), about 15-fold higher than the analogous trend risk of  $1.86 \text{ Sv}^{-1}$  (95% CI 1.36, 2.46) for females (Table 3). This difference is borderline statistically significant ( $p=0.050$ ) (Table 3). These results are much the same without adjustment for the modifying effects (on the ERR) of attained age and age at exposure. Table 4 demonstrates that the optimal adjustment to EAR is for time since exposure.

Table 4 shows that the EAR for males (normalized to 30 years after exposure) is 0.38 /10<sup>4</sup> person-year Sv (95% CI 0.07, 0.89), whereas for females the EAR is about 20-fold higher, 7.25 /10<sup>4</sup> person-year Sv (95% CI 5.53, 9.13), a difference which is highly statistically significant ( $p<0.001$ ). The comparison of EARs between the sexes is much the same without adjustment for time since exposure (Table 4).

There are highly statistically significant trends with dose for male breast cancer mortality ( $p=0.010$ )(Table 5). The breast cancer mortality excess relative risk for males adjusted for the effect of attained age and age at exposure is 9.48 Sv<sup>-1</sup> (95% CI 0.38, 154.90), about 5-fold higher than the analogous trend risk of 1.86 Sv<sup>-1</sup> (95% CI 1.36, 2.46) for females (Table 5). This difference is not statistically significant ( $p>0.2$ ) (Table 5). As for the incidence data, these results are much the same without adjustment for the modifying effects (on the ERR) of attained age and age at exposure. Table 6 demonstrates that the optimal temporal adjustment to EAR is for time since exposure. Table 6 shows that the EAR for males (normalized to 30 years after exposure) is 0.16 /10<sup>4</sup> person-year Sv (95% CI 0.02, 0.39), whereas for females the EAR is about 10-fold higher, 1.53 /10<sup>4</sup> person-year Sv (95% CI 0.86, 2.31), a difference which is highly statistically significant ( $p<0.001$ ). The comparison of EARs between the sexes is much the same without adjustment for time since exposure (Table 6).

Models were also fitted that allowed for separate adjustments by sex for age, time since exposure or age at exposure using relative and absolute risk models. In general there was no evidence of such heterogeneity by sex, save for a borderline significant ( $p=0.094$ ) difference between the time since exposure trends in the mortality relative risk data, with males exhibiting a strong decrease in risk over time compared with a modest increase over time for females (adjustment per decade of time since exposure of 0.11 and 1.26 respectively (data not shown)) (Table 7).

## Discussion

The analyses of this paper suggest that male breast cancer has an excess relative risk that exceeds that for female breast cancer. This elevation of male relative risk compared to female is particularly strong (and borderline statistically significant,  $p=0.05$ ) for breast cancer incidence, where it is about 15-fold, but the elevation is also quite pronounced for breast cancer mortality, about 5-fold (but not statistically significant,  $p>0.2$ ). However, the male breast cancer absolute excess risks are about 10-20 fold less than those for females (and highly statistically significant,  $p<0.001$ ), reflecting the much lower baseline cancer rates for males than for females.

Indeed, the findings of a high ratio of male:female relative excess risks of breast cancer ( $ERR_{male} / ERR_{female}$ ), and low ratio of male:female absolute excess risks ( $EAR_{male} / EAR_{female}$ ), is largely accounted for by the ratio of male:female baseline breast cancer rates ( $CR_{male} / CR_{female}$ ).

Comparison of expressions (1) and (3) would lead one to expect that approximately:

$$\begin{aligned} ERR_{male} / ERR_{female} &\approx (EAR_{male} / CR_{male}) / (EAR_{female} / CR_{female}) \\ &\approx (EAR_{male} / EAR_{female})(CR_{female} / CR_{male}) \end{aligned} \quad (9)$$

The adequacy of this approximation may be judged by the fact that the left hand side of (9) is  $27.68/1.86=14.88$  for incidence (Table 3) and  $9.48/1.86=5.10$  for mortality (Table 5), while the right hand side can be estimated by  $(0.38/7.25)[(320/575,694)/(1/342,504)]=9.98$  for incidence (Table 4, Supplemental Material A Table A2) and  $(0.16/1.53)[(119/893,939)/(2/571,320)]=3.98$  for mortality (Table 6, Supplemental Material A Table A3).

Because of the much lower EARs of male compared with female breast cancer, our findings imply minimal impact on assessments of individual or population breast cancer risk following all

but therapeutic levels of radiation exposure, compared with those using models proposed by national (Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation 2006) and international (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2008) radiation safety committees. Nevertheless, they imply potentially substantial probabilities of causation following modest (e.g., occupational) radiation exposure (Barabanova et al. 1996). The analysis of Supplemental Material A Table A1 suggests that male breast cancers following moderate (occupational) exposure, of 50 mSv, whether incurred at exposure age 35 or 55 years, would be associated with a PC of about 44%, at least five times more than the PC associated with most other highly radiogenic cancer sites, in particular leukemia, and cancers of the stomach, colon, female breast, and brain and central nervous system. However, the calculations for male breast cancer are subject to substantial uncertainties, as may be deduced from the width of the confidence intervals in Table 3. In principle EAR models could also be used to evaluate PC. However, the particular models we developed are not so useful for evaluating this quantity. Because an adequate model of breast cancer in the baseline (unexposed) population would necessarily have to incorporate terms for city (Hiroshima, Nagasaki), it makes them difficult to apply in any context other than to this particular cohort.

There are no strong indications of differences between the sexes in the temporal modifications (by attained age, time since exposure, age at exposure). This is perhaps a function of lack of statistical power due to the very small numbers of cases and deaths in males. There are borderline significant indications that time since exposure modifications in relative risk may differ ( $p=0.09$ ) between the sexes, with the male excess relative risk concentrated in the earlier years of follow-up compared with the female. This does not contradict the pattern shown in Supplemental Material A Table A3, which shows that, as one would expect, all (radiogenic and

other) male breast cancer cases are overwhelmingly concentrated in the later years of follow-up, a simple consequence of the ageing of the cohort.

A detailed comparison of the number of cases and person years of follow-up in the incidence dataset we used and that in the paper of Ron *et al.* (Ron *et al.* 2005) highlights some slight differences (Supplemental Material A Table A2 and Table 1 of Ron *et al.* (Ron *et al.* 2005)). In particular, Ron *et al.* (Ron *et al.* 2005) appear to have an extra case in the lowest breast dose group (0.005-0.5 Sv), we suspect because Ron *et al.* were using an early (and not completely validated) version of the incidence data that was later published by Preston *et al.* (Preston *et al.* 2007). The comparison of numbers of breast cancer deaths (Supplemental Material A Table A3) and incident cases (Supplemental Material A Table A2) by dose group suggests that the breast cancer deaths and incident cases are somewhat different – indeed at least 2 of the breast cancer deaths cannot have been in the incidence dataset, while at least 3 of the incident cases could not have been in the mortality data. Mortality in the LSS is ascertained for those remaining resident in Japan, while incidence is restricted to those people resident in the two cities. There are also temporal differences in follow-up (for mortality 1950-2003, for incidence 1958-1998). This could account for the deaths that do not appear to be incident cases. Given that all the male breast cancer cases occur relatively late (after 1971) (Supplemental Material A Table A4), when effective treatments for breast cancer (male and female) became available, it is quite likely that there will be people who develop breast cancer who do not die from it, thereby accounting for the cancer cases not in the mortality data. Nevertheless, one cannot entirely exclude the possibility that there are errors in the data, and as above there is some evidence of this in the data of Ron *et al.* (Ron *et al.* 2005), which we do not use.

There are very few other studies of male breast cancer in relation to exposure to ionizing radiation. A large US case-control study of male breast cancer, using cases diagnosed from 10 Surveillance, Epidemiology and End Results (SEER) registries, evaluated ionizing radiation as a risk factor, and observed a trend for an increasing risk of breast cancer with an increasing number of self-reported radiographic examinations, which was statistically significant for exams performed between 1933 and 1963, although not for any later period (1964-1987) (Thomas et al. 1994). After radiation therapy, a marginally elevated risk was observed for men first treated in the period 1940-1954, and the risk was somewhat higher when the location of the treatment field resulted in exposure to the breast (Thomas et al. 1994). Evaluation of age and time effects was limited: age at radiation exposure was not statistically significantly related to breast cancer risk, and risk was increased only 20–35 years after radiation exposure. The study has major weaknesses, acknowledged by the authors (Thomas et al. 1994), in particular the low response rate, particularly among the controls (selected by random digit dialing), and the interview-based assessment of past exposures, which may be subject to recall bias. The lack of any estimates of radiation dose, whether due to diagnostic or therapeutic procedures, and the small number of exposed individuals also limit the causal interpretation of these findings.

Women experience menarche and menopause, which are not experienced by men, and the timing of these events appear to influence both the baseline risk of breast cancer (Collaborative Group on Hormonal Factors in Breast 2012) and its sensitivity to radiation induction (Land et al. 1994). Other risk factors for male breast cancer overlap somewhat with those for women, and include obesity and lack of physical activity (Brinton et al. 2008); however, the lack of risk associated with alcohol consumption (Brinton et al. 2008) is in striking contrast to the consistent risk seen in relation to increased alcohol consumption for female breast cancer (Baan et al. 2007; Cao et

al. 2015). Germline mutations in the *BRCA2* gene are a risk factor for both male and female breast cancer, but mutations in the *BRCA1* gene appears to be a risk much more for female breast cancer than for male breast cancer (Ford et al. 1998; Greene 1997; Rizzolo et al. 2013). Mutations in the *PTEN* gene have also been linked to both male and female breast cancer (Fackenthal et al. 2001; Marsh et al. 1998), as additionally have mutations in *CHEK2* (Nevanlinna and Bartek 2006). Male breast cancer has been genetically linked with the *AR* gene (Lobaccaro et al. 1993; Wooster et al. 1992). The differences in male breast cancer etiology that we highlight may have some bearing on the fact that male breast cancer radiation-associated relative risk appears to be substantially higher than that of women, and the weak indications ( $p=0.094$ ) that time since exposure modifications in relative risk may differ between the sexes. However, the small number of cases and deaths in the datasets that we have analyzed argues for a degree of caution in interpretation of this finding.

Nevertheless, our findings build on those of Ron *et al.* (Ron et al. 2005) in suggesting that male breast cancer incidence and mortality is radiogenic, with a degree of excess relative risk that is at least as large as that for female breast cancer. As such, there is a case for the IIAC (Industrial Injuries Advisory Council (IIAC) 2015) and other similar bodies to consider recommending the inclusion of male breast cancer in the list of cancers arising from occupational exposure to ionizing radiation for which compensation may be claimed, as is indeed already the case in the US (United States Department of Labor 2016).

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Table 1: Summary information on numbers of breast cancer cases and deaths by sex in the LSS incidence (Preston et al. 2007) and mortality (Ozasa et al. 2012) data.

	Males	Females	Total
<b>Incidence data<sup>a</sup></b>			
Cases	7	847	854
Persons	32,411	47,769	80,180
Mean age at exposure (years) (range) <sup>b</sup>	20.58 (<0.41, >78.59)	24.29 (<0.37, >81.58)	22.91 (<0.37, >81.58)
Mean attained age (years) (range) <sup>b</sup>	50.19 (<13.90, >107.14)	54.53 (<13.89, >108.44)	52.91 (<13.89, >108.44)
Mean dose (Sv) (range) <sup>b, c</sup>	0.15 (0, >5.46)	0.14 (0, >4.78)	0.15 (0, >5.46)
Person years (PY)	778,687	1,305,300	2,083,987
Rate (/10 <sup>5</sup> PY)	0.90	64.89	40.98
<b>Mortality data</b>			
Cases	6	324	330
Persons	35,687	50,924	86,611
Mean age at exposure (years) (range) <sup>b</sup>	20.28 (<0.45, >85.74)	23.77 (<0.06, >88.63)	22.41 (<0.06, >88.63)
Mean attained age (years) (range) <sup>b</sup>	47.87 (<7.80, >112.14)	52.15 (<7.60, >113.29)	50.49 (<7.60, >113.29)
Mean dose (Sv) (range) <sup>b, c</sup>	0.15 (0, >5.45)	0.15 (0, >5.33)	0.15 (0, >5.45)
Person years (PY)	1,280,800	2,013,490	3,294,290
Rate (/10 <sup>5</sup> PY)	0.47	16.09	10.02

<sup>a</sup>persons that were in either city, with known dose.

<sup>b</sup>person-year weighted mean.

<sup>c</sup>DS02 breast dose, Sv, using neutron relative biological effectiveness of 10.

Table 2. Male breast cancer cases and deaths, and person years of follow-up, by age at exposure and attained age, using data of Preston *et al.* (Preston et al. 2007) and Ozasa *et al.* (Ozasa et al. 2012).

Those in either city with known dose														
Breast cancer incident cases								Person years						
Age at exposure (years)	Attained age (years)							Attained age						
	0-39	40-49	50-59	60-69	70-79	≥80		0-39	40-49	50-59	60-69	70-79	≥80	
0-19		0	1	2	0	0		231816	115956	95032.7	37203.2	1303.64		
20-39		0	0	0	1	1	0	4759.08	29054.8	51543.6	43488.9	27530.9	7270.12	
40-49				0	1	0	1			13154.6	39802	25719.2	11321	
50-59					0	0	0				9918.88	19097.3	7365.45	
60-69						0	0					3177.86	3703.17	
≥70							0						468.543	
Those in either city, possibly with unknown dose														
Breast cancer incident cases								Person years						
Age at exposure (years)	Attained age (years)							Attained age						
	0-39	40-49	50-59	60-69	70-79	≥80		0-39	40-49	50-59	60-69	70-79	≥80	
0-19		0	1	2	0	0		246570	124531	102503	41222.1	1476.71		
20-39		0	0	0	1	2	0	5593.58	33507.8	58876.6	49815.2	31504.5	8223.99	
40-49				0	1	0	2			14604.5	43735.8	28250.9	12297.5	
50-59					0	0	0				10859.6	20725.7	7944.78	
60-69						0	0					3337.86	3823.55	
≥70							0						496.141	
Those in either city with known dose														
Breast cancer deaths								Person years						
Age at exposure (years)	Attained age (years)							Attained age						
	0-39	40-49	50-59	60-69	70-79	≥80		0-39	40-49	50-59	60-69	70-79	≥80	
0-19		0	1	0	1	1		418150	156749	147267	82930.8	15448.1		
20-39		0	0	0	0	1	1	25876.4	55010.5	56421.7	47740.6	34072.7	13716.7	
40-49			0	0	0	0	1		5996.07	46511.2	44057.8	28841.2	13658.9	
50-59				0	0	0	0			5796.36	31886.5	21362.1	8146.53	
60-69					0	0	0				2878.1	11670.6	4166.76	
≥70						0	0					754.569	1685.79	

Table 3. Breast cancer incidence risk by sex, using stratified relative risk model (1), with strata defined by city, sex, age at exposure, attained age, using data of Preston *et al.* (Preston et al. 2007).

Model number	Model/parameter fitted	ERR / Sv (+ 95% CI)	Temporal modifiers (+95% CI)	Deviance	p-value <sup>a</sup>
1	Male breast cancer ( $\alpha_m$ )	19.41 (1.53, 761.30)		53.95	0.003 <sup>b</sup>
2	Female breast cancer ( $\alpha_f$ )	1.50 (1.12, 1.95)		2770.49	<0.001 <sup>b</sup>
3	Male & female breast cancer ( $\alpha$ )	1.54 (1.15, 1.98)		2828.32	<0.001 <sup>b</sup> 0.049 <sup>c</sup>
4	Adjusted for attained age ( $\alpha$ ) Attained age adjustment (per 10 years of age)( $\exp[\beta_1]$ )	1.90 (1.41, 2.50)	0.70 (0.52, 0.90)	2820.14	0.004
5	Adjusted for time since exposure ( $\alpha$ ) Time since exposure adjustment (per 10 years of time since exposure) ( $\exp[\beta_2]$ )	1.62 (1.20, 2.13)	0.89 (0.70, 1.13)	2827.37	0.331 <sup>d</sup>
6	Adjusted for age at exposure ( $\alpha$ ) Age at exposure adjustment (per 10 years of age at exposure) ( $\exp[\beta_3]$ )	1.59 (1.19, 2.05)	0.82 (0.64, 1.02)	2825.28	0.081 <sup>d</sup>
7	Adjusted for attained age and age at exposure ( $\alpha$ ) Attained age adjustment (per 10 years of age) ( $\exp[\beta_1]$ ) Age at exposure adjustment (per 10 years of age at exposure) ( $\exp[\beta_3]$ )	1.89 (1.39, 2.49)	0.71 (0.52, 0.95) 0.97 (0.73, 1.26)	2820.07	0.016 <sup>d</sup> 0.023 <sup>e</sup> 0.802 <sup>f</sup>
8	Adjusted for sex, attained age and age at exposure: males ( $\alpha_m$ ) Adjusted for sex, attained age and age at exposure: females ( $\alpha_f$ ) Attained age adjustment (per 10 years of age) ( $\exp[\beta_1]$ ) Age at exposure adjustment (per 10 years of age at exposure) ( $\exp[\beta_3]$ )	27.68 (1.81, 90.16 <sup>g</sup> ) 1.86 (1.36, 2.46)	0.70 (0.51, 0.94) 0.99 (0.75, 1.30)	2816.24	0.050

<sup>a</sup>unless otherwise indicated the p-value represents the improvement in fit over the model in the row immediately above it.

<sup>b</sup>p-value of improvement in fit over the null model, with no terms in dose.

<sup>c</sup>p-value of improvement in fit of model allowing for different dose coefficients (  $\alpha_m, \alpha_f$  ) by gender, over model 3, in other words what is obtained by comparing the combined fit of models 1 and 2 with that of model 3.

<sup>d</sup>p-value of improvement in fit over model 3.

<sup>e</sup>p-value of improvement in fit over model 6.

<sup>f</sup>p-value of improvement in fit over model 4.

<sup>g</sup>Wald-based CI.

Table 4. Breast cancer incidence risk by sex, using absolute risk model (3), using data of Preston *et al.* (Preston et al. 2007).

Model number	Model/parameter fitted	EAR / $10^4$ person year Sv (+ 95% CI)	Temporal modifiers (+95% CI)	Deviance	<i>p</i> -value <sup>a</sup>
1	Null model	-		3168.32	
2	Male & female breast cancer ( $\alpha$ )	2.36 (1.49, 3.36)		3119.66 <sup>b</sup>	<0.001
3	Male breast cancer ( $\alpha_m$ )	0.35 (0.02, 0.88)		3054.49	<0.001
	Female breast cancer ( $\alpha_f$ )	7.07 (5.38, 8.92)			
4	Adjusted for attained age ( $\alpha$ )	2.28 (1.38, 3.30)		3118.49	0.279 <sup>c</sup>
	Attained age adjustment (per 10 years of age) ( $\exp[\beta_1]$ )		1.12 (0.91, 1.40)		
5	Adjusted for time since exposure ( $\alpha$ )	2.38 (1.45, 3.43)		3114.00	0.017 <sup>c</sup>
	Time since exposure adjustment (per 10 years of time since exposure) ( $\exp[\beta_2]$ )		1.46 (1.07, 2.02)		
6	Adjusted for age at exposure ( $\alpha$ )	2.40 (1.51, 3.43)		3119.49	0.676 <sup>c</sup>
	Age at exposure adjustment (per 10 years of age at exposure) ( $\exp[\beta_3]$ )		0.95 (0.75, 1.19)		
7	Adjusted for attained age and time since exposure ( $\alpha$ )	2.37 (1.41, 3.44)		3114.00	0.059 <sup>c</sup>
	Attained age adjustment (per 10 years of age) ( $\exp[\beta_1]$ )		1.01 (0.79, 1.29)		0.933 <sup>d</sup>
	Time since exposure adjustment (per 10 years of time since exposure) ( $\exp[\beta_2]$ )		1.45 (1.03, 2.08)		0.034 <sup>e</sup>
8	Adjusted for sex, time since exposure: males ( $\alpha_m$ )	0.38 (0.07, 0.89)		3042.84 <sup>b</sup>	<0.001 <sup>d</sup>
	Adjusted for sex, time since exposure: females ( $\alpha_f$ )	7.25 (5.53, 9.13)			
	Time since exposure adjustment (per 10 years of time since exposure) ( $\exp[\beta_2]$ )		1.41 (1.16, 1.71)		

<sup>a</sup>unless otherwise indicated the *p*-value represents the improvement in fit over the model in the row immediately above it.

<sup>b</sup>indications of lack of convergence.

<sup>c</sup>*p*-value of improvement in fit over model 2.

<sup>d</sup>*p*-value of improvement in fit over model 5.

<sup>e</sup>*p*-value of improvement in fit over model 4.

Table 5. Breast cancer mortality risk by sex, using stratified relative risk model (1), with strata defined by city, sex, age at exposure, attained age, using data of Ozasa *et al.* (Ozasa et al. 2012).

Model number	Model/parameter fitted	ERR / Sv (+ 95% CI)	Temporal modifiers (+95% CI)	Deviance	p-value <sup>a</sup>
1	Male breast cancer ( $\alpha_m$ )	8.88 (0.60, 92.34)		48.34	0.010 <sup>b</sup>
2	Female breast cancer ( $\alpha_f$ )	1.56 (0.96, 2.34)		1804.10	<0.001 <sup>b</sup>
3	Male & female breast cancer ( $\alpha$ )	1.64 (1.02, 2.42)		1854.49	<0.001 <sup>b</sup> 0.152 <sup>c</sup>
4	Adjusted for attained age ( $\alpha$ ) Attained age adjustment (per 10 years of age)( $\exp[\beta_1]$ )	2.10 (1.21, 3.35)	0.79 (0.54, 1.07)	1852.21	0.131
5	Adjusted for time since exposure ( $\alpha$ ) Time since exposure adjustment (per 10 years of time since exposure) ( $\exp[\beta_2]$ )	1.37 (0.72, 2.19)	1.26 (0.95, 1.76)	1851.91	0.108 <sup>d</sup>
6	Adjusted for age at exposure ( $\alpha$ ) Age at exposure adjustment (per 10 years of age at exposure) ( $\exp[\beta_3]$ )	1.78 (1.03, 2.72)	0.54 (0.33, 0.79)	1842.94	<0.001 <sup>d</sup>
7	Adjusted for attained age and age at exposure ( $\alpha$ ) Attained age adjustment (per 10 years of age) ( $\exp[\beta_1]$ ) Age at exposure adjustment (per 10 years of age at exposure) ( $\exp[\beta_3]$ )	1.85 (0.93, 3.10)	0.96 (0.62, 1.43) 0.55 (0.33, 0.82)	1842.90	0.003 <sup>d</sup> 0.840 <sup>e</sup> 0.002 <sup>f</sup>
8	Adjusted for sex, attained age and age at exposure: males ( $\alpha_m$ ) Adjusted for sex, attained age and age at exposure: females ( $\alpha_f$ ) Attained age adjustment (per 10 years of age) ( $\exp[\beta_1]$ ) Age at exposure adjustment (per 10 years of age at exposure) ( $\exp[\beta_3]$ )	9.48 (0.38, 154.90) 1.86 (0.96, 3.10)	0.92 (0.58, 1.38) 0.57 (0.34, 0.85)	1841.51	0.239

<sup>a</sup>unless otherwise indicated the p-value represents the improvement in fit over the model in the row immediately above it.

<sup>b</sup>p-value of improvement in fit over the null model, with no terms in dose.

<sup>c</sup>p-value of improvement in fit of the model allowing for different dose coefficients (  $\alpha_m, \alpha_f$  ) by gender, over model 3, in other words what is obtained by comparing the combined fit of models 1 and 2 with that of model 3.

<sup>d</sup>p-value of improvement in fit over model 3.

<sup>e</sup>p-value of improvement in fit over model 6.

<sup>f</sup>p-value of improvement in fit over model 4.

Table 6. Breast cancer mortality risk by sex, using absolute risk model (3), using data of Ozasa *et al.* (Ozasa et al. 2012).

Model number	Model/parameter fitted	EAR / 10 <sup>4</sup> person year / Sv (+ 95% CI)	Temporal modifiers (+95% CI)	Deviance	p-value <sup>a</sup>
1	Null model	-		2221.65	
2	Male & female breast cancer ( $\alpha$ )	0.58 (0.27, 0.97)		2203.91 <sup>b</sup>	<0.001
3	Male breast cancer ( $\alpha_m$ )	0.13 (-0.04 <sup>c</sup> , 0.43)		2185.32	<0.001
	Female breast cancer ( $\alpha_f$ )	1.63 (0.98, 2.40)			
4	Adjusted for attained age ( $\alpha$ )	0.57 (0.24, 0.98)		2198.63	0.022 <sup>d</sup>
	Attained age adjustment (per 10 years of age)( $\exp[\beta_1]$ )		1.37 (1.05, 1.88)		
5	Adjusted for time since exposure ( $\alpha$ )	0.53 (0.17, 0.96)		2185.18 <sup>b</sup>	<0.001 <sup>d</sup>
	Time since exposure adjustment (per 10 years of time since exposure) ( $\exp[\beta_2]$ )		2.11 (1.50, 3.48)		
6	Adjusted for age at exposure ( $\alpha$ )	0.59 (0.24, 0.98)		2202.94	0.324 <sup>d</sup>
	Age at exposure adjustment (per 10 years of age at exposure) ( $\exp[\beta_3]$ )		0.83 (0.48, 1.19)		
7	Adjusted for attained age and time since exposure ( $\alpha$ )	0.53 (0.18, 0.97)		2185.07 <sup>b</sup>	<0.001 <sup>d</sup>
	Attained age adjustment (per 10 years of age) ( $\exp[\beta_1]$ )		0.94 (0.63, 1.35)		
	Time since exposure adjustment (per 10 years of time since exposure) ( $\exp[\beta_2]$ )		2.20 (1.43, 3.87)		<0.001 <sup>f</sup>
8	Adjusted for sex, time since exposure: males ( $\alpha_m$ )	0.16 (0.02, 0.39)		2159.70	<0.001 <sup>e</sup>
	Adjusted for sex, time since exposure: females ( $\alpha_f$ )	1.53 (0.86, 2.31)			
	Time since exposure adjustment (per 10 years of time since exposure) ( $\exp[\beta_2]$ )		1.83 (1.45, 2.40)		

<sup>a</sup>unless otherwise indicated the p-value represents the improvement in fit over the model in the row immediately above it.

<sup>b</sup>indications of lack of convergence.

<sup>c</sup>Wald-based CI.

<sup>d</sup>p-value of improvement in fit over model 2.

<sup>e</sup>p-value of improvement in fit over model 5.

<sup>f</sup>p-value of improvement in fit over model 4.

Table 7. Evidence of variation by sex in the modifying adjustment to the excess relative risk or excess absolute risk by attained age, time since exposure, age at exposure in the breast cancer incidence and mortality data of Preston *et al.* (Preston et al. 2007) and Ozasa *et al.* (Ozasa et al. 2012), respectively. Breast cancer risk modeled using expressions (2) and (4)

	<i>p</i> -value <sup>a</sup>	
	Incidence data	Mortality data
<b>Relative risk model (2) with univariate adjustment for either: (a) attained age; (b) time since exposure; or (c) age at exposure</b>		
Model adjusted for sex, attained age x sex compared with model adjusted for sex, attained age only	>0.2 <sup>b</sup>	0.206
Model adjusted for sex, time since exposure x sex compared with model adjusted for sex, time since exposure only	0.816	0.094
Model adjusted for sex, age at exposure x sex compared with model adjusted for sex, age at exposure only	0.499	0.715
<b>Relative risk model (2) with adjustment for attained age, age at exposure</b>		
Model adjusted for sex, age at exposure, attained age x sex compared with model adjusted for sex, age at exposure, attained age	>0.2 <sup>b</sup>	>0.2 <sup>b</sup>
Model adjusted for sex, age at exposure x sex, attained age compared with model adjusted for sex, age at exposure, attained age	0.462	0.685
Model adjusted for sex, age at exposure x sex, attained age x sex compared with model adjusted for sex, age at exposure, attained age	>0.2 <sup>b</sup>	>0.1 <sup>b</sup>
<b>Absolute risk model (4) with adjustment for time since exposure</b>		
Model adjusted for sex, time since exposure x sex compared with model adjusted for sex, time since exposure	>0.2 <sup>b</sup>	>0.2 <sup>b</sup>

<sup>a</sup> the *p*-value represents the improvement in fit over the model with specified temporal adjustments and with adjustment for gender in the linear dose coefficients (  $\alpha_m, \alpha_f$  ) obtained by adding interactions by gender to the temporal modification terms.

<sup>b</sup>indications of non-convergence.